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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,224	06/22/2001	Jay M. Short	DIVER1150-6	8097

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,224	SHORT ET AL.	
	Examiner	Art Unit	
	Jehanne S Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55,88-96,101,103,106,107,110-112 and 115-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55,88-96,101,103,106,107,110-112 and 115-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/5/2004 has been entered.

2. The examiner reviewing your application at the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Jehanne Sitton in art unit 1634.

3. Claims 42-55, 88-96, 101, 103, 106, 107, 110-112, and 115-133 are pending in the instant application. The amendments and arguments have been thoroughly reviewed but were found insufficient to place the instant application in condition for allowance. The following rejections are newly applied and constitute the complete set being presently applied to the instant application. The following office action is NON-FINAL.

4. The rejections under 35 USC 102 and 103 made in the previous office action are moot in view of the amendments to the claims.

Priority

5. The following claims are awarded the priority of the filing date of 5/22/1996 of parent application 08/651,572 as the disclosure of the claims finds support in the parent application: 42, 94, 111, 120-122 and 123. All remaining pending claims are awarded the priority date of 6/22/2001, the filing date of the instant application.

Claims 43-55 for methods of making variants do not find support in any of the parent applications as such methods of mutagenesis are not disclosed in any of the parent applications. Accordingly, claims 43-55 are awarded a priority date of 6/22/2001.

Claims 88-92, 95, 96, 105, 107, 110, 112, 115, 116, 124-127, and 131-133 are drawn to methods of modifying *any* small molecule. The specification provides no definition for such recitation. The parent '572 application does not recite a method for modifying any small molecule but only discloses hydrolysis of cellulose and the modification of carboxymethylcellulose (CMC) using SEQ ID NO: 1. While the parent specification teaches that SEQ ID NO: 1 can be used for the degradation of cellulose for the conversion of plant biomass into fuels and chemicals, for use in detergents, the textile industry, in animal feed, in waste treatment, and in the fruit juice/brewing industry, such recitation does not provide any specific support for the modification of any small molecules outside the scope of cellulose and CMC. The recitation of small molecule is not specifically defined in the instant specification to be limited to cellulose or CMC, and therefore encompasses any small molecule, including any carbohydrate, lipid, peptide, nucleic acid, or organic or inorganic molecule. As such, the claims are not supported by the originally filed parent application and are awarded the benefit of the filing of the instant application: 6/22/2001.

Claims 93, 101, 103, 117-119 and 128-130 specifically recite consecutive nucleotide fragments as well as % identities which do not find specific support in the parent application. It is noted that some claims reciting methods of modifying small molecules, set forth in the preceding paragraph, also recite nucleic acids which have specific consecutive nucleotide fragments as well as % identities which do not find specific support in the parent application and are denied the benefit of the priority date of the parent application for these reasons as well.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 42-55, 88-96, 101, 103, 106, 107, 110-112, and 115-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are drawn generally to making variants of a polypeptide encoded by SEQ ID NO: 1 with any endoglucanase activity by either modifying SEQ ID NO: 1 or obtaining a nucleic acid already encoding a variant of SEQ ID NO: 1 with at least anywhere from 70-99% identity to SEQ ID NO: 1 or a variant of SEQ ID NO: 1 with at least 30, 40, or 75 consecutive residues with a sequence having anywhere from 70-99% identity to SEQ ID NO: 1, and possessing any endoglucanase activity, and modifying the variant, wherein the objective of all embodiments is to modify the nucleic acid by modifying one or more nucleotides to another nucleotide, deleting one or more nucleotides, or adding one or more nucleotides to obtain a variant encoding an enzyme with any endoglucanase activity. The claims are further drawn to using such a peptide to modify any small molecule. The specification does not define endoglucanase activity to be limited to the hydrolysis of the beta 1,4, glycosidic bond in cellulose, and thus the term broadly encompass any other activity of the polypeptide of SEQ ID NO: 1 including antigenic reactivity. Therefore, variants of the polypeptide encoded by SEQ ID NO: 1 encompasses polypeptides that

bind to antibodies that the wildtype protein bind to, which broadly encompasses polypeptides with similar domains or signatures with the wildtype protein (SEQ ID NO: 2) but that do not necessarily catalyze the hydrolysis of the beta 1,4, glycosidic bond in cellulose. Additionally, the specification does not define what is encompassed by the recitation of "small molecule" and therefore the claims broadly encompass the modification of any "small" molecule which includes any carbohydrate, lipid, peptide, nucleic acid, or organic or inorganic molecule by any 'variant' of SEQ ID NO: 2 with the requisite % identity and consecutive residues. The specification, however, does not teach how to make the broadly recited variants, nor which 'small' molecules would be predictably modified by such a broad scope of variants.

The amount of direction or guidance:

The specification provides inadequate guidance to allow the skilled artisan to determine, without undue experimentation, which of the myriad of possible deletion, substitution, or insertion mutations of SEQ ID NO: 1 would encode a polypeptide which would be likely to retain biological activity. While the specification teaches how to generally make variants of proteins (see for example page 19, 3rd para; page 20, 2nd full para; pages 25-26; page 27 2nd and 3rd para; pages 33-36, page 42, pages 48-52), the use of computer programs to determine sequence homology (see pages 62-67) and generally how to screen for variants (see for example page 22; pages 25-26), the specification provides no guidance regarding the effects of substitution and/or insertion or deletion mutations on enzymes with carboxymethyl cellulase activity, or the ability to hydrolyze the beta 1,4 glycosidic bond in cellulose, the domain structure of the protein, the location of the active site or sites of interaction with cofactors or regulatory

molecules, the molecular basis of the protein's activity, its secondary and tertiary structure, the importance of domains in maintaining activity, etc. Accordingly, the skilled artisan would not be able to determine which proteins encoded by nucleic acids with the required % identity or consecutive basis, or capability to hybridize under the disclosed hybridization conditions, would predictably retain *any* general or specific endoglucanase activity, including for example, carboxymethyl cellulase activity. Further, the specification provides no guidance as to which 'small' molecules would be capable of modification by the broadly recited variants set forth in the claims.

Presence and absence of working examples:

The specification provides no working examples of making any variants of SEQ ID NO: 1 which encode an enzyme with any broad endoglucanase activity or with the ability to hydrolyze the beta 1,4, glycosidic bond in cellulose or with carboxymethyl cellulase activity, nor does the specification provide any working examples of modifying any small molecule with any such variants.

The state of the prior art and the predictability or unpredictability of the art:

The art specifically addresses the unpredictability of modifying endoglucanases by site directed mutagenesis to attain a molecule with any specific activity or ability to modify any cellulose substrate. For example, Pons (Pons et al; The J. of Biol. Chemistry; vol. 20, pages 13006-13012, 1997) teaches making mutants of 1,3 1,4 glucan glucanhydrolase from *B. licheniformis*, and teaches that some mutants, M58A notably, had surprising effects that were

unpredictable from a simple structural analysis since the side chain of Met-58 does not interact with the substrate or with any essential catalytic residues in the 3-dimensional structure of the free enzyme (se page 13011, col. 2). Further, Pons specifically teaches that another remarkable mutant, N57A with increased thermostability, was obtained and that the effect of this mutation as well as the M58A mutation were unpredictable with current knowledge of protein structure/function relationships (see page 13011, col. 2, last para). Additionally, Zhang (Zhang and Wilson, Journal of Biotechnology, vol. 57, pages 101-113, 1997) teaches that surface residue mutants of endoglucanase E2 from *Thermomonospora fusca* had significant changes on the substrate specificity of the enzyme (see table 1, and page 109, col 1, first para). Zhang teaches that 12 different surface residues were found in sugar binding sites and conserved in endoglucanases in family 6 and were mutated to non sugar binding residues. Zhang teaches that most of the mutants did not show major changes in activity, but that some do, the most striking of which was W16I which is from form the active site (see page 111, col. 1, last full para). Thus Zhang illustrates that actual mutations must be made to determine the effect of a particular residue. Further, while Zhang teaches that while a G87A mutation had a larger effect on activity that a G86A mutation, as predicted, it was also predicted that Cys mutations would increase activity, but did not (see page 112, col. 1). Thus Zhang also illustrates the unpredictability with regard to mutations in endoglucanases and the resulting effect on endoglucanase activity as well as the fact that the effect on substrate specificity is elucidated by actual mutagenesis, and not only by predictive analysis.

The art further teaches of the unpredictability of using structural homologies between proteins to predict function. Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711,

1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is, protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col. 2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also cites RecA which contains a DNA binding domain, a multimerization domain and additional sites that bind regulatory proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that

subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered. The art specifically teaches, that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

It would require undue experimentation for one of skill in the art to practice the invention as broadly as it is claimed. The instant specification provides insufficient guidance to allow the skilled artisan to predict beforehand, the effects of particular deletion, substitution and/or insertion mutations of the claimed SEQ ID NOS. Given that the art specifically teaches of the unpredictability of making modifications in endoglucanases and obtaining a desired activity, teaches that actual modifications are needed to determine the effect of a specific residue on the activity and substrate specificity of endoglucanases, and teaches that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein, the skilled artisan would have to perform extensive trial and error manipulations, the effect of each mutation being unpredictable on the activity and substrate specificity of the

resulting protein variant, to determine which proteins would be predictably encoded by nucleic acids which possessed the recited % identity, contiguous fragments, or ability to hybridize to other nucleic acids under the recited conditions. While the specification generally teaches how to make variants of proteins and how to screen for activity, such is a teaching of how to find particular proteins which fall within the scope of the instantly pending claims, not how to make them. However, the requirements of 35 USC 112/first paragraph are that the specification be enabling for one of skill in the art to make and use the claimed invention. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Indefinite

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 90-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 90-92 lack sufficient antecedent basis for the recitation of 'the library' in claim 90. No library is recited in any of the claims from which claim 90 depends. Accordingly, it is unclear if the recitation of "the small molecules" in claim 90 refers to modified or unmodified small molecules.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 88, 89, 93, 95, 96, 101, 103, 106, 107, 110, 112, 115, 117-119,.and 124-133 rejected under 35 U.S.C. 102(b) as being anticipated by Lam (Lam et al; US Patent 6,074,867, 6/13/2000).

Lam teaches the sequence of the endoglucanase encoded by the sequence of SEQ ID NO: 1, as well as the protein of SEQ ID NO: 2 which are identical to the sequences of SEQ ID NO: 1 and SEQ ID NO: 2 recited in the instant specification. With regard to the claims directed to making variants, such claims encompass making variants of SEQ ID NO: 1. Lam inherently teaches making variants of a polypeptide encoded by SEQ ID NO: 1 in teaching non naturally occurring variants of the polypeptide encoded by SEQ ID NO: 1 (see col. 7, line 60- col. 9, line 22). With regard to the claims drawn to methods of modifying small molecules, Lam teaches that the polypeptide encoded by SEQ ID NO: 1 can be used for the degradation of cellulose for the hydrolysis o the beta 1,4 glycosidic bonds in CMC (col. 13, lines 24-29; col. 7, lines 22-32).

Conclusion

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-

0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton
Primary Examiner
Art Unit 1634
11/1/04